Chelation of Cadmium without Increased Renal Cadmium Deposition

by M. George Cherian*

Cadmium (Cd) is mainly accumulated in liver and kidney bound to metallothionein (MT) and excreted very slowly from the body. In chronic exposure, Cd is gradually transported from liver to kidney; the renal toxic effects appear when renal Cd concentration exceeds the critical concentration. In order to prevent the Cd-induced renal disease, it is important to control the movement of Cd to the kidney and its renal deposition. However, the chelation of Cd from liver is difficult because of the high affinity of intracellular MT for Cd. A number of chelating agents containing both carboxyl and thiol groups were able to mobilize and excrete Cd more easily in a short time (1/2 hr) after Cd exposure than longer times (24 hr), after MT synthesis. The renal deposition of Cd increased on BAL (2,3-dimercaptopropanol) treatment a short time (1/2 hr) after Cd exposure. However, it was observed that if BAL was administered 24 hr after Cd exposure, it could mobilize Cd from hepatic MT and increase the biliary excretion of Cd without any increase in renal Cd concentration. Studies using a number of structurally related thiols (mono-, di- and trithiols) showed that the major structural requirement for *in vivo* chelation of Cd from intracellular MT were the vicinal thiol groups on an aliphatic chain, and lipophilicity. BAL was the most effective of all the compounds studied and it did not mobilize Cd to the kidney, when most of the intracellular Cd was bound to MT. Furthermore, a delayed treatment with BAL or DTPA (diethylenetriamine pentaacetic acid) after synthesis of MT resulted in an increase in fecal or urinary excretion of Cd in rat model experiment. The injection of DTPA in combination with BAL was more effective in decreasing the concentration of Cd and MT in liver and kidney from rats chronically exposed to Cd than injection of BAL alone. Since DTPA cannot enter the cell, it may be acting extracellularly in removing the Cd. The results of these studies suggest that the specific intracellular binding of Cd to MT is an important factor in protecting kidney, the critical organ, in the effective chelation of Cd by BAL.

The development of an effective chelation therapy for cadmium (Cd) has been extremely difficult because of the special features in the pharmacokinetics and toxicity of Cd compounds. Unlike other metals, Cd has an unusually long biological half-time in human and is excreted very slowly from the body (1). After absorption from the respiratory and gastrointestinal tracts, Cd is mainly accumulated in liver and kidney bound to metallothionein (MT), a low molecular weight sulfur-rich intracellular protein (2,3). The low excretion of Cd from the body may be closely related to its specific intracellular binding to MT. Although acute and chronic Cd poisonings in humans are not common, there are isolated cases of chronic Cd poisoning in workmen and people living in certain polluted areas (4–7). However, there are no specific biological indicators for either Cd exposure or toxicity. In Cd-exposed people, the chronic toxicity such as renal dysfunction will appear only after a long lag period of several years, and when a critical concentration of renal Cd is reached (8,9). It is known that there is a gradual mobilization of Cd from liver to kidney and the major critical organ in chronic Cd toxicity is the kidney (10–12). Therefore, it is important to consider all the factors involved in the renal deposition of Cd to develop an effective chelation therapy for Cd and to prevent the Cd induced renal disease. In this report, some of the research work on the biliary excretion and chelation of Cd in experimental animals from our laboratory will be summarized.

Our approach has been to study the normal excretory pathways of cadmium and to develop

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methods to increase the biliary excretion of Cd. Thus the hepatic Cd could be removed before it reaches kidney, the critical organ in chronic cadmium toxicity. To achieve these goals, we have made use of various chelating agents, containing both carboxyl and thiol groups. A number of studies were undertaken on chelation therapy for cadmium, soon after the second world war. Most of these studies were acute Cd exposure experiments and were carried out by Gilman and coworkers in the U.S.A. (13), Friberg's group in Sweden (14) and Eybl's group in Czechoslovakia (15). All of these studies concluded that it is difficult to mobilize Cd without acute renal damage. Therefore, chelation of Cd was considered to be contraindicated. However, little was known two decades ago about either the excretory pathways of Cd or the specific intracellular binding of Cd to MT (16). The induced synthesis of MT within a few hours after exposure to Cd has a marked effect on the pharmacokinetics and toxicity of Cd (3). Since most of the Cd becomes intracellular soon after its absorption and is specifically bound to MT in several organs within a few hours after exposure, these important factors should be considered for therapeutic chelation of Cd. Thus, Cd differs from a number of other nonessential metals such as lead and mercury in its toxicity.

Biliary Excretion of Cd and Involvement of MT

Previous studies (16,17) from our laboratory suggested that biliary excretion of Cd may be an important excretory pathway in a single high dose exposure. The dose-dependent increase in biliary excretion of Cd was similar to that of manganese salts (18) but was different from mercury compounds (19). Although the major intracellular form of Cd is protein bound, the form of Cd in bile has been partially characterized as a glutathione conjugate. It is also known that the induction of MT synthesis by injection of metals can reduce the diffusible form of Cd in the body and thereby decrease the biliary excretion of Cd (20,21). Thus, the synthesis of MT and binding of Cd to this intracellular protein has a marked effect on the pharmacokinetics of Cd. Subsequent studies from other laboratories have confirmed these results and extended them to other divalent metals (22,23). Preinjection of experimental animals with zinc and copper salts also decreased the biliary excretion of Cd (24) and this effect also may be due to the induced synthesis of hepatic MT.

Thus, the biliary excretion of Cd is mainly regulated by two factors: the intracellular specific binding ligands such as MT and the level of exposure. This may be unique to Cd because of its intracellular localization and specific binding to MT within a few hours after Cd exposure. Because of the high affinity of Cd for this protein, it is difficult to mobilize intracellular Cd from MT and to increase the biliary excretion of Cd with chelating agents in chronic Cd exposure (24).

Effect of Chelating Agents before and after MT Synthesis on Biliary Transport of Cadmium

A systematic study (24) was undertaken in our laboratory to investigate the effects of various chelating agents containing carboxyl or/and thiol groups on mobilization of Cd from rats exposed to Cd salts. The role of MT in this process was also studied. A number of chelating agents such as 2,3-dimercaptopropanol (BAL), DL-penicillamine and dithioerythritol increased the biliary excretion of Cd within a short time (½ hr) after Cd exposure. All these compounds contained thiol groups and the dithiol (BAL) was the most effective of all the compounds studied. However, these thiol compounds also increased the deposition of Cd in the kidney when administered within 30 min of Cd exposure, i.e., before the synthesis of MT. These results showed little therapeutic value for mercaptans in acute Cd exposure and were similar to earlier reports (13,14). Under similar experimental conditions, chelating agents such as ethylenediaminetetraacetic acid (EDTA) and nitrilotriacetic acid (NTA) containing carboxyl groups were able to increase the urinary excretion of Cd with a small decrease in both hepatic and renal Cd deposition. Therefore, chelating agents containing carboxyl groups may be useful in removing Cd from the body soon after acute exposures, and these results are in agreement with previous reports (25–28). Another polyamino polycarboxylate, diethylenetriaminepentaacetic acid (DTPA), and its derivative, Puchel, also have been found to be effective mobilizing agents for Cd (29–31). Since most of the carboxylic acid containing complexing agents used in most of these studies are hydrophilic, their action is limited to the extracellular compartment. Therefore, they may prevent the cellular uptake of Cd while lipophilic compounds may increase Cd uptake into the cell soon after exposure of Cd. Thus, each chelating agent has different effects on the distribution and excretion of Cd in acute

Cd exposures before the induced synthesis of MT (24,26,27).

Several studies (32–34) have demonstrated that subcutaneous injection of mice with precomplexed Cd salts with NTA or sodium tripolyphosphate (STPP) increased the acute toxicity of Cd, as measured by mortality. The enhanced acute toxicity is probably due to the hepatotoxicity of these complexes of Cd. A similar acute renal toxicity is reported after injection of Cd complexed with thiol compounds such as cysteine (35). Complexes of Cd with thiol compounds increased the renal deposition of Cd as compared to the Cd salts alone (24). These studies suggest that mobilization of Cd, soon after exposure may increase the risk for development of both acute hepatotoxicity and renal damage. Therefore the chelating agents should be used with great caution in acute Cd exposures.

As discussed earlier, the cellular uptake of Cd is a rapid process and the intracellular Cd remains bound to MT within a few hours after exposure. MT is a metal sequestering protein and it can bind with 7 g-atoms of Cd very strongly (log β_3 for Cd = 25.5). The Cd atoms in MT are tetrahedrally coordinated to cysteinyl residues in two distinct polynuclear metal clusters, as indicated by ^{113}Cd-NMR studies. Because of this strong specific intracellular binding, there is little excretion of Cd in urine or bile after the synthesis of MT. Most of the chelating agents that were effective in mobilization of Cd soon after exposure showed little effect on Cd excretion or tissue distribution when administered after the synthesis of MT (24). The only compound which increased the biliary and urinary excretion of Cd after MT synthesis was BAL and it showed a dose-dependent response. However, the efficiency of BAL in increasing the excretion of Cd was sharply reduced with the synthesis of MT and the binding of Cd to MT. Although BAL was less effective in mobilization of Cd from MT than from other proteins, the renal level of Cd did not increase when the chelation was started after MT synthesis (36). Preliminary studies on partial characterization of the biliary form of Cd suggest the formation of a Cd-BAL complex before the synthesis of MT. But the major form of Cd in the bile when chelated with BAL after MT synthesis was associated with a 10,000 molecular weight fraction (24). Further studies suggested that this was not a simple Cd-BAL complex or Cd-MT, but may be a polymerized metabolite of BAL or a ternary complex with MT and similar proteins. The formation of different types of Cd binding complexes in vivo in bile after injection of BAL
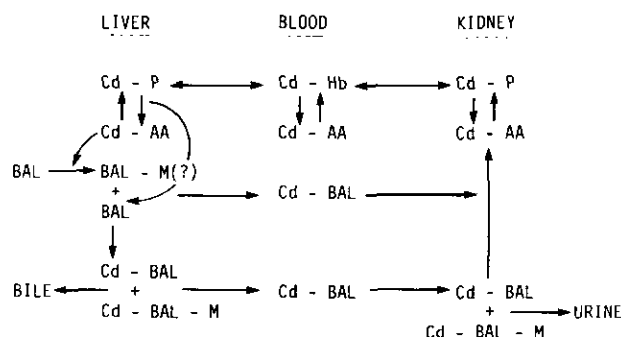

FIGURE 1. Chelation of cadmium with BAL before MT synthesis and the forms of cadmium in bile, blood and tissues. Cd–P, Cd bound to protein; Cd–AA, Cd bound to aminoacids; Cd–Hb, Cd bound to hemoglobin; Cd–BAL, Cd complexed with BAL; Cd–BAL–M, Cd bound to BAL metabolite.
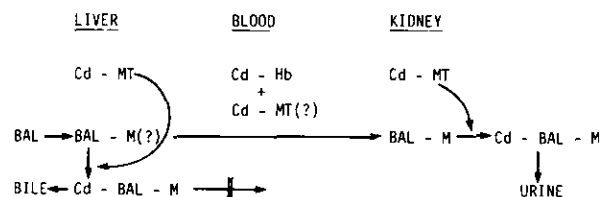

FIGURE 2. Chelation of cadmium with BAL after MT synthesis and the forms of cadmium in bile, blood and tissues. Cd–MT, Cd bound to metallothionein; Cd–Hb, Cd bound to hemoglobin; BAL–M, metabolites of BAL; Cd–BAL–M, Cd bound to metabolites of BAL.

before and after synthesis of MT can be explained by the postulated schemes shown in Figures 1 and 2.

Since Cd has high affinity for amino acids, peptides and other macromolecules, no ionic Cd is found either in the cells or biological fluids. As shown in Figure 1, before the synthesis of MT, Cd is bound nonspecifically to proteins (Cd-P) or forms diffusible complexes with amino acids (Cd-AA) in both liver and kidney. In the blood, Cd is bound to hemoglobin (Cd-Hb) or amino acids (Cd-AA). If BAL is injected at this stage, it may only be partly converted into its metabolites (BAL-M). A major portion of this compound may remain intact and directly form a Cd-BAL complex which can be detected in both urine and bile. Our results suggest the excretion of Cd-BAL complex in bile if BAL is injected to Cd-exposed rats before the synthesis of MT (36). A part of the Cd-BAL complex will also be transported to kidney. This may result in increased accumulation of Cd in the kidney.

If the BAL treatment is delayed until the syn-

1. $CH_2 - CH_2 - CH_3$
   $\quad\;\; |$
   $\quad\;\; SH$

   1-Propanethiol

2. $CH_2 - CH - CH_3$
   $\quad\;\; | \quad\;\; |$
   $\quad\;\; SH \quad SH$

   1,2-Dimercaptopropane

3. $CH_2 - CH_2 - CH_2$
   $\quad\;\; | \quad\quad\quad |$
   $\quad\;\; SH \quad\quad\; SH$

   1,3-Dimercaptopropane

4. $CH_2 - CH - CH_2$
   $\quad\;\; | \quad\;\; | \quad\;\; |$
   $\quad\;\; SH \quad SH \quad SH$

   1,2,3-Trimercaptopropane
   (Propane trithiol)

5. $CH_2 - CH - CH_2$
   $\quad\;\; | \quad\;\; | \quad\;\;\;\; |$
   $\quad\;\; SH \quad SH \quad SO_3,Na$

   2,3-Dimercapto-1-propane-
   sulfonic acid (sodium salt)

6. $CH_2 - CH - CH_2$
   $\quad\;\; | \quad\;\; | \quad\;\; |$
   $\quad\;\; SH \quad SH \quad OH$

   2,3-Dimercapto-1-propanol
   (BAL)

7. $CH_2 - CH - CH_2$
   $\quad\;\; | \quad\;\; | \quad\;\; |$
   $\quad\;\; SH \quad OH \quad SH$

   1,3-Dimercapto-2-propanol

8. $CH_2 - CH$
   $\quad\;\; | \quad\;\; |$
   $\quad\;\; SH \quad SH$

   1,2-Dimercaptoethane
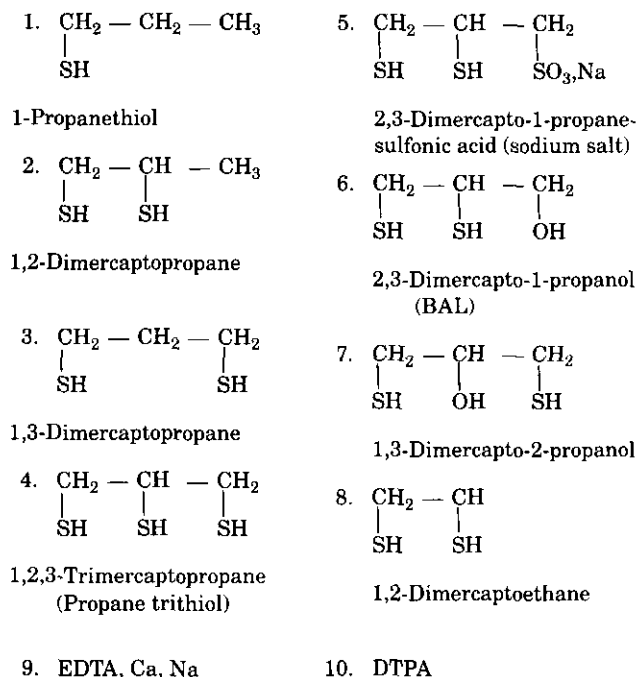
9. EDTA, Ca, Na

10. DTPA

FIGURE 3. Chelating agents.

thesis of MT, most of the intracellular Cd will be exclusively bound to MT in both liver and kidney (Fig. 2). Under this condition, most of the BAL which has entered the liver and kidney will be metabolized and part of the Cd from MT can be removed as Cd-BAL-M. This complex does not enter the blood circulation and there is no increase in the renal Cd levels. Because of its high polarity, this complex is specifically eliminated through bile canaliculi into the bile and also filtered into urine without any reabsorption at the tubules. Thus, chelation of Cd after synthesis of MT will result in decreased Cd levels in both liver and kidney.

The mode of action of BAL in increasing the biliary Cd excretion without any increased renal deposition of Cd after MT synthesis is not clear. We believe that it is related to the formation of different types of Cd complexes with BAL or its metabolites in the liver before and after synthesis of MT. The dose of BAL used in the treatment is also important for effective chelation after MT synthesis (36,37). Further studies (36) using di-mercaptosuccinic acid (DMSA) and 2,3-dimer-capto-1-propanesulfonic acid (DMPS) which are structurally similar to BAL showed that these compounds were not effective in mobilizing Cd bound to MT in the liver. The lack of effect of these compounds can be explained by their hydro-philic property which may prevent them from

entering the cell and reaching the site of deposition of cadmium.

These studies show that MT plays an important role in the specific binding of intracellular Cd, and in protection of the kidney during chelation of hepatic Cd by BAL. These conclusions are contrary to a recent report (39), which claims to demonstrate that MT plays a minimal role in determining chelator efficacy with respect to Cd. Failure to demonstrate the effect of MT in that report is not surprising, as the conclusions are based on the use of a single chelator, DTPA. It is well known that Cd-MT is an exclusively intra-cellular complex, while the hydrophilic chelator DTPA cannot enter the cell, and binds only extra-cellular Cd as a result. A few minutes after exposure, Cd is present intracellularly, bound to proteins and other ligands. The amount of diffusible Cd is minimal. Successful removal of Cd following MT synthesis, then, depends on delivery of chelator to the intracellular location, and successful competition with MT ($\log \beta_3$ for Cd = 25.5). DTPA fails to meet the former criterion.
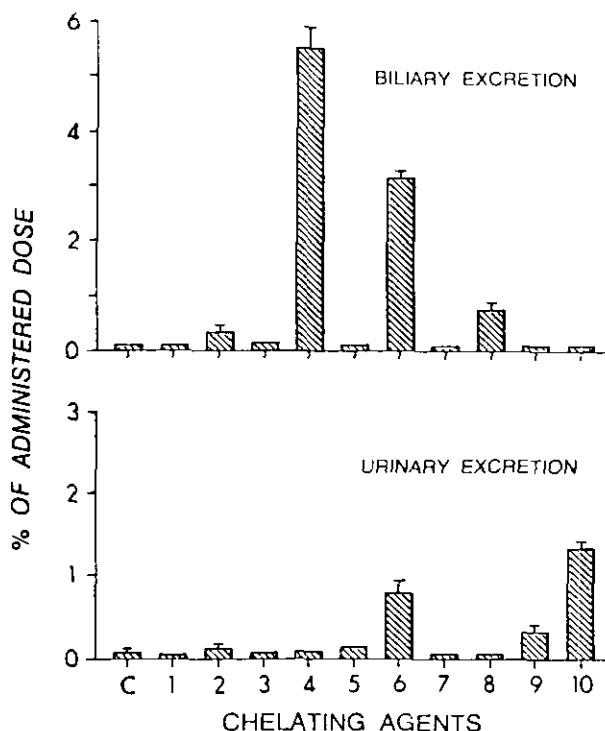

FIGURE 4. Biliary and urinary excretion of Cd following chelation. Rats were injected intravenously with 1 mg Cd/kg as $^{109}CdCl_2$ and 24 hr later, the bile duct was cannu-lated. They were injected intraperitoneally with either propylene glycol (c-control) or chelating agents, 400 μmole/kg. The numbers (1–10) indicate the chelating agents as shown in Fig. 3. The bile and urine samples were collected for 3 hr. The results are means ± SD from six rats in each group.

Structural Requirement for Chelation of Cd from MT *in Vivo*

Since BAL was one of the few compounds effective in mobilizing Cd from MT, we have compared the ability of several structurally related mono-, di- and trithiols to mobilize Cd from hepatic MT. In this study, chelators containing carboxyl groups (EDTA and DTPA) were also included (Fig. 3). The details of these studies are published elsewhere (*38*). All the chelating agents were administered in equimolar amounts (400 µmole/kg) as intraperitoneal injections to rats which were pretreated with $CdCl_2$ (1 mg/kg), 24 hr earlier. The bile and urine samples were collected for 3 hr after injection of chelating agents.

The results showed (Fig. 4) that all the dithiol compounds containing adjacent thiol groups could mobilize Cd from hepatic MT and increase the biliary excretion of Cd while none of the other compounds with nonadjacent thiol groups or one single thiol group was effective. Compounds with a third carbon substitution, such as the -OH group in BAL or the -SH group in propanetrithiol were more effective than 1,2-dimercaptopropane. However, propanetrithiol was extremely toxic and may not have any therapeutic value. DMPS was not effective because of its hydrophilic property. BAL also increased the urinary Cd excretion under these experimental conditions. Both EDTA and DTPA increased the urinary excretion of Cd without any effect on the biliary Cd excretion. These results show that the structural requirements for effective chelation of Cd from MT in Cd-exposed rats are the vicinal thiol groups and lipophilic properties of the chelating agents.

Recent studies (*40,41*) from our laboratory suggest that injection of BAL and/or DTPA to rats pretreated with $CdCl_2$, at least 24 hr earlier, can increase the fecal and urinary excretion of Cd without any increase in renal Cd levels. There was a marked decrease in the whole-body retention and hepatic levels of Cd. These studies also show that the Cd excreted through the bile is not reabsorbed from the gastrointestinal tract. After mobilization of Cd, there was a decrease in the MT levels in both liver and kidney.

Although these results are promising, more work should be undertaken to develop better and nontoxic chelating agents to mobilize Cd from the body without any renal damage in both acute and chronic exposures. The need for the search of specific metal mobilizing agents and their prophylactic use in excessive exposure to toxic metals are discussed in detail in a recent review article by Aposphian (*42*).

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